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EXAMINER	
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ART UNIT	PAPER NUMBER
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NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-75* is/are pending in the application.

4a) Of the above claim(s) *60-66 and 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-70* is/are rejected.

7)☒ Claim(s) *67-69* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/26/2009, are acknowledged and entered. Claims 22-24, 28-33, and 39-59 have been cancelled by Applicant. Claims 60-75 are newly added. Claims 60-75 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 22-24, 28-33, and 39-59 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Election/Restrictions

Newly submitted claims 60-66 and 71-75 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: originally filed claims 1-13 were drawn to a method of treating tumors comprising the following steps: (A) administering a tumor-treating effective amount of an agent to a subject; and (B) exposing the subject to a tumor-treating effective amount of radiation. Originally filed claims 14-20 were drawn to a method of hypomethylating genes. Originally filed claim 21 was drawn to a composition comprising CldC and 4-N-methylamino FdC. The Examiner required an election of one invention as well as an election of species (see Office Action mailed 5/9/2006). Applicants elected Group I, claims 1-13, and the combination CldC and tetrahydrouridine. In response to the Non-Final Office Action mailed 9/25/2008, Applicant cancelled all pending claims and submitted new claims drawn to numerous distinct inventions. Only those methods recited in newly added claims 67-70 are drawn to methods of treating tumors comprising the same steps as those in the elected invention (*i.e.*, administration of CldC and tetrahydrouridine followed by exposure of the subject to radiation). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 60-66 and 71-75 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

Claims 67-69 are objected to because of the following informalities: the word "an" appears to be missing between the words "in" and "amount" in line 3 of each respective claim. The claims should read "...in an amount...", not "...in amount...". Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd Paragraph – New Ground of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are unclear with respect to what is being administered. Claims 67-68 recite a method consisting essentially of administering to a patient CldC in an amount "sufficient to produce elevated levels of CldUMP and CldU coadministered with an amount of tetrahydrouridine". Claim 69 recites a method consisting essentially of administering to a patient CldC in an amount "sufficient to produce elevated levels of CldUMP and CldU coadministered with an amount of cytidine deaminase inhibitor". Claim 70 recites a method consisting essentially of administering to a patient escalating or high doses of CldC to produce "elevated levels of CldUMP and CldU, coadministered with H4U". The claims are unclear as to whether only CldC is being administered to the patients or whether CldC is being administered with tetrahydrouridine. One interpretation of the claims is that only CldC is being administered and that "coadministered" with tetrahydrouridine is descriptive of the amount of CldC administered, i.e., CldC is administered in an amount sufficient to produce elevated levels of CldUMP and CldU coadministered with an amount of tetrahydrouridine.

Claim Rejections - 35 USC § 112 – 1st Paragraph – New Ground of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-70 are are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to methods consisting essentially of administering to a subject CldC and radiation. The following claim limitations are not supported in the originally filed disclosure and thus constitute New Matter:

1) "...*consisting essentially of* administering to said patient CldC..." (claims 67-69);

2) "...exposing said tumor to a dose of radiation that *alone is ineffective in producing tumor control*" (claim 68); and

3) "...*consisting essentially of* administering to said patient escalating or high doses of CldC..." (claim 70).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

As a first matter, Applicant does not have written basis for the claimed "consisting essentially of" language. See MPEP 2111.03.

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original)

In the present case, Applicant has not described the basic and novel characteristics of the claimed invention such that the skilled artisan would recognize from the disclosure what materials or

steps are intended to be excluded from the claims by the recited "consisting essentially of" language. Applicant describes his invention as related to a method of treating tumors by administering agents before and/or during a course of radiation treatment (page 1). The agents include CldC administered with a cytidine deaminase inhibitor (tetrahydrouridine or zebularine) or CldC administered without a cytidine deaminase inhibitor, when combined with new sources, new schedules of radiation, and/or new categories of tumors (id.). Applicant further discloses that he previously found it necessary to administer PALA, FdC, tetrahydrouridine, and CldC to achieve clinically relevant radiosensitization. Whether administration of PALA and/or FdC would materially affect the basic and novel characteristics of the claimed invention is not clear from Applicant's disclosure.

Secondly, nowhere does Applicant disclose exposing tumors to a dose of radiation that alone is ineffective in producing tumor control. The only discussion of doses of radiation in found at page 10 where Applicant discloses that a dose of 70 Gy will be "as effective" as a dose of 210 or 280 Gy against tumors or a "much lower dose of radiation such as 23.3 Gy" can be provided and obtain tumor kill normally obtained with 70 Gy or 93 Gy. There is no discussion that 70 Gy or 23.3 Gy is alone "ineffective in producing tumor control" as recited in the instant claims.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102 – New Ground of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67 and 69-70 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Greer** (WO 85/01871; Published May 9, 1985).

Instant claims 67 and 69-70 recite methods of "achieving tumor control in at least one human tumor in a patient" consisting essentially of administering CldC and radiation. In one

interpretation of the claims a patient is administered CldC and tetrahydrouridine (H_4U) in amounts effective to produce elevated levels of CldUMP and CldU and the tumor is then exposed to a dose of radiation. In another interpretation of the claims, the patient is exposed to CldC in an amount effective to produce elevated levels of CldUMP and CldU and the tumor is then exposed to a dose of radiation.

Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract; page 3, lines 4-14). Further, Greer teaches that when CldC is administered with H_4U, CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 16-28). The reference thus explicitly teaches administration of CldC and tetrahydrouridine to a patient with a tumor followed by exposing the tumor to radiation. Also see Table 1 at page 41 of Greer, wherein on days WED and THURS, CldC and H_4U are administered prior to radiation.

The invention of Greer provides therapeutic materials and procedures for treating solid tumors using X-ray or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-15). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy.

Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds. Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference, it is clear that Greer also unequivocally teaches administering a

combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14). While such therapy may be *enhanced* by co-administration with an inhibitor of pyrimidine biosynthesis, the fact remains that 5-chloro-2'-deoxycytidine and tetrahydrouridine are alone effective to sensitize tumors to radiation when administered without such an inhibitor of pyrimidine biosynthesis.

The instantly claimed methods only require that a tumor be sensitized to radiation when a patient is administered 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by an effective level of radiation. Table 1 of Greer (page 41) explicitly teaches administering to a patient CldC + H4U followed by radiation wherein none of PALA, FdC, 4-N-methyl FdC, and FdU are administered to the patient (days WED and THURS of the "Standard Protocol" in Table 1).

It is clear from the Greer reference that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine is effective to sensitize tumors to irradiation. As such, Greer clearly anticipates the claimed method of treating tumors comprising sensitizing tumors to radiation by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine and exposing a patient to an effective level of radiation.

With regard to the amounts of CldC and/or tetrahydrouridine as recited in the instant claims, Greer teaches dosages of these agents at page 18, Table II. In the absence of evidence to the contrary, such doses of CldC are "sufficient to produce elevated levels of CldUMP and CldU" and the doses of tetrahydrouridine are effective to "prevent toxicity of the CldC" as recited in the instant claims.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Greer** (WO 85/01871; Published May 9, 1985).

Greer teaches as applied to claims 67 and 69-70 *supra*. Greer does not explicitly teach administering radiation at a dose that is alone ineffective in producing tumor control. However, Greer does teach that the radiation dose will either be the same or 1/4 or 3/4 the dose given to patients not receiving the pretreatment sensitization schedule (page 17, lines 16-19).

As such, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have exposed tumors sensitized to radiation with CldC and tetrahydrouridine a dose of radiation that is lower that the dose given to patients not receiving the pretreatment sensitization with CldC and tetrahydrouridine. One skilled in the art would have been imbued with at least a reasonable expectation that a dose of radiation that alone is ineffective in producing tumor control would be made effective to produce tumor control when administered to tumors that have been sensitized to radiation as taught in Greer.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 67-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 4,894,364. Although the

conflicting claims are not identical, they are not patentably distinct from each other because the methods of the '364 patent encompass the administration of CldC and tetrahydrouridine to sensitize tumors to radiation. The courts have determined that "consisting essentially of" can be construed as an equivalent of "comprising".

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).

It is the examiner's position that the inclusion of other agents as in some claims of the '364 patent would not materially affect the basic and novel characteristics of the instantly claimed methods. Further, the court has held that:

> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, *e.g.*, *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Examiner finds no such "clear indication" in the specification or the claims of what the basic and novel characteristics actually are. Thus, the interpretation of the instant claims to be drawn to methods "comprising" the recited steps is appropriate.

> If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964).

Thus, the language of the instant claims allows for the inclusion of other active agents in the claimed methods thereby rendering the instant methods unpatentable over claims 1-8 of the '364 patent.

Claims 67-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6,933,287. Although the conflicting claims are not identical, they are not patentably distinct from each other because the courts have determined that "consisting essentially of" can be construed as an equivalent of "comprising".

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).

It is the examiner's position that the inclusion of 4-N-methyl FdC as required in the methods of the '287 patent would not materially affect the basic and novel characteristics of the instantly claimed methods. Further, the court has held that:

> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, *e.g.*, *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Examiner finds no such "clear indication" in the specification or the claims of what the basic and novel characteristics actually are. Thus, the interpretation of the instant claims to be drawn to methods "comprising" the recited steps is appropriate.

> If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964).

Thus, the language of the instant claims allows for the inclusion of 4-N-methyl FdC in the claimed methods thereby rendering the instant methods unpatentable over claims 1-18 of the '287 patent.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614